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## **Exercise for all cystic fibrosis patients: is the evidence strengthening?**

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**Abstract:** PURPOSE OF REVIEW Regular physical activity and exercise have become important components of cystic fibrosis care. This review summarizes the recent evidence in favour of regular exercise in cystic fibrosis that has accumulated over the past years. **RECENT FINDINGS** Several recently published small randomized-controlled trials and observational studies have added to our knowledge on positive effects of exercise training on pulmonary function and aerobic fitness in cystic fibrosis. Relevant outcomes, such as body posture, health-related quality of life and rate of hospitalization, are increasingly studied. Findings from these studies suggest that exercise might also be beneficial for these outcomes. So far, many important questions such as the best way of integrating exercise in cystic fibrosis care and the determination of the optimal strategies for training and motivation remain mostly unanswered. **SUMMARY** Over the past years, evidence for the beneficial effects of regular exercise on lung health and aerobic exercise capacity is strengthening. Despite the fact that most of the knowledge is based on small studies, the observed effects are encouraging and there is no reason why exercise should not be implemented in all patients' care.

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# Exercise for all cystic fibrosis patients: is the evidence strengthening?

Helge Hebestreit<sup>a</sup>, Susi Kriemler<sup>b</sup>, and Thomas Radtke<sup>b</sup>

## Purpose of review

Regular physical activity and exercise have become important components of cystic fibrosis care. This review summarizes the recent evidence in favour of regular exercise in cystic fibrosis that has accumulated over the past years.

## Recent findings

Several recently published small randomized-controlled trials and observational studies have added to our knowledge on positive effects of exercise training on pulmonary function and aerobic fitness in cystic fibrosis. Relevant outcomes, such as body posture, health-related quality of life and rate of hospitalization, are increasingly studied. Findings from these studies suggest that exercise might also be beneficial for these outcomes. So far, many important questions such as the best way of integrating exercise in cystic fibrosis care and the determination of the optimal strategies for training and motivation remain mostly unanswered.

## Summary

Over the past years, evidence for the beneficial effects of regular exercise on lung health and aerobic exercise capacity is strengthening. Despite the fact that most of the knowledge is based on small studies, the observed effects are encouraging and there is no reason why exercise should not be implemented in all patients' care.

## Keywords

fitness, health-related quality of life, physical activity, pulmonary function

## INTRODUCTION

Over the last 20–30 years, regular physical activity and exercise have been increasingly recommended for people with cystic fibrosis. This recommendation is based on beneficial effects of exercise in the general population, some evidence from smaller randomized-controlled trials and longitudinal studies that found maximal aerobic capacity to be one of the strongest predictors of mortality in cystic fibrosis, and from a few studies on potential mechanisms underlying the beneficial effects of exercise on cystic fibrosis (pulmonary) disease.

This review will summarize the evidence that has accumulated over the past years in favour of regular exercise in cystic fibrosis while highlighting the most intriguing findings. Some of these studies have addressed novel outcomes and/or augmented our understanding of how exercise might lead to improved lung function.

## HOW MUCH EVIDENCE IS THERE THAT REGULAR EXERCISE IMPROVES FITNESS AND PULMONARY FUNCTION?

### Evidence from randomized-controlled exercise interventions

A Cochrane systematic database review on the effects of physical training for cystic fibrosis published in 2008 concluded that there was some limited evidence for beneficial effects of physical exercise on

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## KEY POINTS

- Exercise improves aerobic exercise capacity and probably lowers the rate of decline in pulmonary function.
- Motivation for exercise and long-term adherence to regular training and sufficient habitual physical activity remain major challenges in cystic fibrosis care.
- High-quality randomized controlled studies with long-term follow-up are needed to increase the evidence base for the effects of exercise on bone health, exacerbations and cystic fibrosis-related diabetes.

exercise capacity, strength and lung functions based on seven randomized-controlled studies [1<sup>■</sup>]. Since then, several relatively small randomized-controlled trials using different approaches have been published [2<sup>■</sup>,3<sup>■</sup>,4–6]. The studies by Hebestreit *et al.* [2<sup>■</sup>] and Kriemler *et al.* [3<sup>■</sup>] both assessed effects of physical training over 6 months and reported improvements in aerobic exercise capacity (expressed as peak oxygen uptake,  $\text{VO}_2\text{peak}$ ) and lung functions in the intervention compared with the control group. In two studies from Santana-Sosa *et al.* [4,5] an 8-week supervised aerobic and strength-training programme including inspiratory muscle training in one study resulted in improvements in  $\text{VO}_2\text{peak}$  and muscle strength. Likewise, a home-based aerobic and strength training programme over 3 months did result in improved upper limb strength [6]. In two other studies from a Brazilian group, the intervention was based on manuals with instructions on home-based aerobic and strength training given to patients. One study observed changes in posture and the other study found improved muscle strength but no effects on aerobic exercise capacity or lung function [7,8].

### Additional evidence from observational studies in cystic fibrosis

Although large randomized-controlled trials on the effects of physical exercise training in cystic fibrosis are still lacking, observational studies may supplement the evidence available from smaller trials. Schneiderman *et al.* [9<sup>■</sup>] followed 212 young patients with cystic fibrosis over 9 years. In this sample, a greater increase in reported habitual physical activity was associated with a slower decline in forced expiratory volume in 1 s ( $\text{FEV}_1$ ) ( $-1.63\%$  per year) after adjusting for sex, baseline age and  $\text{FEV}_1$ , mucoid *Pseudomonas aeruginosa* and cystic fibrosis-related diabetes. The group of patients with an increase in activity above average had an annual loss in  $\text{FEV}_1$  of  $1.39\%$  compared with  $1.90\%$  in those whose change

in activity was below average. In another study, Col-laco *et al.* [10<sup>■</sup>] analyzed data from more than 1000 participants of the U.S. CF Twin Sibling study. Regular exercise participation was assessed by questionnaires at baseline and subsequent rate of decline in  $\text{FEV}_1$  was calculated from repeated measurements. In a mixed model analysis, adjusting for age at diagnosis, age at assessment of exercise habits, sex and baseline  $\text{FEV}_1$ , regular exercise was associated with a reduced decline in  $\text{FEV}_1$  and body mass index (BMI) z-score in adults. However, for children aged 10–17 years at baseline, no such association was detected, suggesting that regular exercise may possibly be more important for cystic fibrosis patients with advanced disease.

### IS THERE EVIDENCE FOR ‘THE BEST’ EXERCISE MODE, DURATION AND INTENSITY IN CYSTIC FIBROSIS?

Most randomized-controlled trials in the past focussed on aerobic-type activities for intervention. The randomized-controlled trial reported by Kriemler *et al.* [3<sup>■</sup>] assessed the effects of 6 months of either aerobic or strength training compared with no additional exercise training in mostly adult people with cystic fibrosis. Interestingly, both aerobic training and strength training were associated with similar improvements in  $\text{FEV}_1$ , forced vital capacity (FVC), and aerobic exercise capacity. Thus, both training modes might be regarded as similarly effective in cystic fibrosis. However, in a separate publication of the same study assessing the longitudinal associations between physical fitness and health-related quality of life (HRQoL), strength training had a negative effect on the scale ‘Vitality’ [11<sup>■</sup>]. Furthermore, strength training lowered static hyperinflation, whereas aerobic training did not. Kriemler *et al.* [3<sup>■</sup>] speculated that improvements in FVC with strength training might be because of a decrease in hyperinflation in this group.

In people with cystic fibrosis and severe pulmonary impairment, standard exercise training might not be feasible. Gruber *et al.* [12] could show that an individual interval-training programme on the treadmill with supplemental oxygen five times per week over a period of 6 weeks can improve submaximal and maximal aerobic exercise capacity in patients with severe disease (mean  $\text{FEV}_1$   $25.5 \pm 7.5\%$  predicted comparable to improvements with conventional exercise training in patients with less severe disease (mean  $\text{FEV}_1$   $31.6 \pm 4.2\%$  predicted). These data support the fact that even patients with severe lung impairment can benefit from an individually tailored exercise intervention.

The optimal exercise training intensity for people with cystic fibrosis remains to be defined. Most of the

training studies that were able to improve aerobic exercise capacity used moderate exercise intensities at 50% of  $\text{VO}_2\text{max}$  or 60–85% of maximum heart rate [2<sup>■</sup>,3<sup>■</sup>,4,5]. Recently, Wheatley *et al.* [13<sup>■</sup>] evaluated the acute effects of exercise versus pharmacological treatment with albuterol on diffusion capacity and bronchodilation in mildly affected cystic fibrosis patients by the use of different exercise intensities (low, moderate and vigorous). Light intensity exercise did not result in changes of diffusion capacity nor in any degree of bronchodilation. Vigorous exercise – although showing the highest increase in diffusion capacity for nitric oxide – was associated with airflow restriction. Moderate intensity exercise, however, was found to be the optimal training intensity for individuals with cystic fibrosis. Fifteen minutes of moderate intensity exercise on a stationary bike lead to a doubling of diffusion capacity of nitric oxide and a relevant bronchodilation (+23%) compared with baseline. Albuterol administration induced a similar bronchodilation 1–2 h after application, but no change in diffusion capacity.

### **DOES REGULAR EXERCISE IMPROVE HEALTH-RELATED QUALITY OF LIFE?**

In cystic fibrosis,  $\text{VO}_2\text{peak}$  is a major determinant of HRQoL and positively correlates with several HRQoL scales [11<sup>■</sup>]. Likewise, improvements in  $\text{VO}_2\text{peak}$  are associated with a better health perception and less weight problems [11<sup>■</sup>]. Thus, it is not surprising that all randomized-controlled studies on exercise training in cystic fibrosis published recently assessed HRQoL as important patient-reported outcome [2<sup>■</sup>,3<sup>■</sup>,4–7]. Surprisingly, only one of these studies was able to identify significant improvements in HRQoL scales with physical training after 6 months of intervention [2<sup>■</sup>], while many others lasting 2–6 months were not [4–7]. Several reasons may contribute to the absence of effects on HRQoL. First, exercise capacity did not change in some studies [6,7] indicating that the exercise intervention may not have been of a sufficient intensity. In two studies [4,5], HRQoL was analyzed as summary score of all domains, which may have obscured the effects of exercise on single HRQoL scales. It has been shown that the associations between exercise capacity and HRQoL are not of equal strength among the different scales [11<sup>■</sup>].

### **ARE THERE EFFECTS OF REGULAR EXERCISE ON BODY POSTURE?**

Recently, Schindel *et al.* [8] investigated the effects of physical training on posture. A manual with instructions for aerobic exercises and stretching

was provided to a group of patients and recommendations were reinforced by telephone calls every 2 weeks. After 3 months, the intervention group showed a decrease in cervical lordosis, thoracic kyphosis, lumbar lordosis, lateral chest distance and abdominal protrusion compared with the control group using a photographic method that was analyzed with commercial software.

### **DOES PHYSICAL TRAINING REDUCE THE NEED FOR INTRAVENOUS ANTIBIOTICS AND/OR THE NUMBER OF HOSPITALIZATIONS?**

Respiratory exacerbations are one of the most common reasons for hospitalizations in cystic fibrosis. Perez *et al.* [14] investigated the associations  $\text{VO}_2\text{peak}$  and risk for hospitalization in 77 children ( $10 \pm 4$  years) with mild-to-moderate cystic fibrosis lung disease over 3 years. Thirty-one percent of the participants were hospitalized once with a mean in-hospital stay of  $10 \pm 4$  days. In univariate Cox regression analysis, FEV1, FVC and  $\text{VO}_2\text{peak}$  and oxygen saturation ( $\text{SaO}_2$ ) at peak exercise were associated with an increased risk of hospitalization. In a multivariate regression model,  $\text{VO}_2\text{peak}$  remained the only independent predictor of hospitalization. In line with these findings, Urquhart *et al.* [15] reported a reduction in days on intravenous antibiotics with a supervised exercise programme in a small sample of children with cystic fibrosis followed longitudinally, yet, their study had no control group. As these observed associations between physical fitness and rate of hospitalization do not imply a causal relationship, it has to be determined in the future whether improvements in fitness through regular exercise can result in fewer exacerbations, less hospital admissions or less need for intravenous antibiotics.

### **IS REGULAR EXERCISE EQUALLY EFFECTIVE FOR EVERYBODY?**

Age, sex, nutritional status, pulmonary impairment or the types of mutation have a known impact on the responses to regular exercise and physical training. However, there is some evidence that people with high serum immunoglobulin (Ig) G levels and colonization with *Pseudomonas aeruginosa* improved  $\text{VO}_2\text{peak}$  less than other patients performing regular exercise [16].

### **NOVEL THERAPIES AND EFFECTS ON EXERCISE CAPACITY**

In recent years, advances have been made in novel mutation-specific therapies in cystic fibrosis. After

the first of these drugs – ivacaftor – became available to patients with at least one G551D mutation and severely impaired pulmonary function, patients reported an improved fitness shortly after the treatment was started [17]. Three cases were published on the effects of ivacaftor on aerobic exercise capacity in patients with F508del/G551D mutations [18,19]. Quon *et al.* [18] evaluated the effects of twice-daily ivacaftor treatment (150 g) over 10 weeks in a male adult with severe cystic fibrosis lung disease (FEV<sub>1</sub> 39% predicted). After ivacaftor treatment, FEV<sub>1</sub> and lung diffusion capacity for carbon monoxide (CO) improved by 16 and 22%, respectively, and a marked increase was observed in exercise duration, peak workrate and VO<sub>2</sub>peak by 33, 25 and 14%, respectively. The main reason for this striking improvement was thought to be attained through impressive improvements in bronchial wall thickening and mucus plugging visualized by computer tomography (CT) scan that translated in improved ventilation with reduced expiratory flow limitations at exercise. In another study, Saynor *et al.* [19] reported on the effects of ivacaftor treatment in two teenagers with cystic fibrosis and preserved lung function (FEV<sub>1</sub>, 92 and 108% predicted) over 20 weeks. Cardiopulmonary exercise testing on a cycle ergometer was performed 6 and 12 weeks after initiation of treatment. After 12 weeks, improvements in VO<sub>2</sub>peak were 30% in one patient, whereas no meaningful change was observed in the other patient. The latter patient, however, did not perform maximally during 12-week postassessment. The improvement of exercise capacity in the first patient was associated with improved oxygen delivery and muscle oxygen extraction resulting in increased cardiac output, whereas cardiac output remained unchanged in the second patient. Whether an improved aerobic exercise capacity with ivacaftor therapy can be observed in most patients receiving this treatment, whether improvements merely reflect changes in ventilation and pulmonary function and whether ivacaftor treatment modulates training responses will require systematic studies.

### APPROACHES AND CHALLENGES TO IMPROVE PARTICIPATION AND ADHERENCE TO PHYSICAL EXERCISE

Motivating people to become or to stay physically active is sometimes challenging, not only in cystic fibrosis. A recent Cochrane review evaluated the effect of treatment to increase participation in physical activity in cystic fibrosis and came to the conclusion that there is very limited evidence that activity counselling and exercise advice are effective to promote participation in physical activity [20].

However, only few randomized-controlled studies have addressed this relevant outcome.

Video game activities are becoming increasingly popular and recent research has evaluated whether these ‘new’ modalities can be considered as alternatives to conventional exercise training [21–23]. Active video games were well tolerated in one study [23] and comparable with vigorous physical activity in adults [21] and light-to-moderate physical activity in children with cystic fibrosis [22]. However, whether these modalities have the potential to sustain beneficial effects on aerobic fitness and improve training adherence in the long-term remains highly speculative based on rather disillusioning results in health populations.

Further, in a small study, Cox *et al.* [24] evaluated an 8-week internet-based programme to monitor and encourage participation in physical activity in adults with cystic fibrosis. The programme was found to be feasible and acceptable; however, further data are needed to assess the usefulness of internet-based applications and apps to increase physical activity participation in the long term.

### FUTURE PERSPECTIVES

Although physical activity and regular exercise are advocated by most cystic fibrosis centres, many questions still remain unanswered today: What is the optimal training mode, duration and intensity for people with cystic fibrosis? What is the optimal setting and approach to motivate patients for life-long exercise? And does exercise affect outcomes other than fitness and pulmonary function? Lately, the largest exercise trial ever performed in cystic fibrosis, the international multicentre randomised-controlled study ACTIVATE-CF (clinical.trials.gov; NCT01744561), has started and will probably be able to increase the current knowledge and evidence base on the effects of exercise training in people with cystic fibrosis. There is a clear need for high-quality randomized-controlled studies with sufficient numbers of patients and well chosen, objectively measurable, reproducible and sensitive outcome measures. These should include also rarely studied but patient-relevant outcomes such as bone health, diabetic control and exacerbations.

### CONCLUSION

Over the past years, exercise training has become an accepted and valued component of cystic fibrosis care. Unfortunately, well-conducted prospective randomized-controlled exercise training studies are still rare in cystic fibrosis, and longer term



follow-up although widely considered important is rarely done. Future studies should not only focus on the main intervention effects, but also on studying the mediating mechanisms and potential moderators, or subgroup effects, although we acknowledge that cystic fibrosis is a rare disease. Only then can we start to answer the question: 'For whom, how and under what circumstances does which intervention work?' Despite the fact that there is substantial heterogeneity on the effects of exercise training between studies, the evidence is strengthening that regular exercise can slow the rate of decline in pulmonary function, improve aerobic exercise capacity and possibly enhance HRQoL.

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## Conflicts of interest

*There are no conflicts of interest.*

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- of special interest
- of outstanding interest

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